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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/918,702	07/31/2001	Nissim Benvenisty	1822/113	3581

2101 7590 08/08/2003

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EXAMINER
CROUCH, DEBORAH

ART UNIT	PAPER NUMBER
1632	12

DATE MAILED: 08/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/918,702	BENVENISTY, NISSIM	
	Examiner	Art Unit	
	Deborah Crouch, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-47* is/are pending in the application.

4a) Of the above claim(s) *1-7 and 18-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 July 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 11 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Applicant's arguments filed June 2, 2003 in paper no. 11 have been fully considered but they are not persuasive. The amendment has been entered.

The proposed drawing correction filed on June 2, 2003 has been disapproved because it is not in the form of a pen-and-ink sketch showing changes in red ink or with the changes otherwise highlighted. See MPEP § 608.02(v).

Claim 17 is objected to as being improperly dependent on claim 1.

Applicant's amendments to Claim 8 have overcome the rejection made under 35 U.S.C. 112, second paragraph in the previous office action mailed January 29, 2003.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 8-10 and 17 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Keller (1995) Current Opinion in Cell Biology 7, 862-869 in view of Thomson et al (1998) Science 282, pp. 1145-1147 for reasons set forth in the previous office action mailed January 29, 2003.

Keller teaches the production of embryoid bodies by culturing ES cells in the absence of feeder cells or LIF, and to culture them in liquid media or methylcellulose containing media on bacterial Petri dishes (page 862, col. 2, lines 5-10). The ES cells grown in these conditions will not adhere to the surface of the culture dish, that the ES cells are grown in suspension, and subsequently form EB's (page 862, col. 2, lines 10-13). In some protocols the EB's are dissociated to form a monolayer and grown on stromal cells to develop into hematopoietic lineage cells (page 863, figure 1(b)). This co-culture provides at least one exogenous factor. Keller teaches that embryoid bodies, when cultured for extended periods

of time can generate cells of the hematopoietic, endothelial, muscle and neuronal lineages (page 863, col. 1, lines 5-9). The formation of specific lineages is the formation of specific cell types.

Thomson teaches the production of human embryonic stem cells line, H9 (page 1145, col. 2, parag. 1, line 6-11; and page 1145, col. 2, parag. 1, line 22 to col. 3, line 5). Thomson offers motivation in stating that human ES cells will provide for human transplantation therapies, and that while substantial advances need to be made in the directed differentiation of human ES cells, progress in the directed differentiation of mouse ES cells to neurons, hematopoietic cells and cardiomyocytes has been made (page 1146-1147, bridg. parag.). Motivation comes from Keller teaching that embryoid bodies provide an approach for defining the earliest steps of commitment from respective precursor population (pages 866-867, bridg. sentence).

Claims 8, 11, 13, 15 and 16 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Keller (1995) Current Opinion in Cell Biology 7, 862-869 and Wobus et al (1987) Cell Diff. 20 (Suppl), 81S in view of Thomson et al (1998) Science 282, pp. 1145-1147 for reasons set forth in the previous office action mailed January 29, 2003.

Keller teaches the production of embryoid bodies by culturing ES cells in the absence of feeder cells or LIF, and to culture them in liquid media or methylcellulose containing media on bacterial Petri dishes (page 862, col. 2, lines 5-10). The ES cells grown in these conditions will not adhere to the surface of the culture dish, that the ES cells are grown in suspension, and subsequently form EB's (page 862, col. 2, lines 10-13). In some protocols the EB's are dissociated to form a monolayer and grown on stromal cells to develop into hematopoietic lineage cells (page 863, figure 1(b)). This co-culture provides at least one exogenous factor. Keller teaches that embryoid bodies, when cultured for extended periods of time can generate cells of the hematopoietic, endothelial, muscle and neuronal lineages

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Thomson teaches the production of human embryonic stem cells line, H9 (page 1145, col. 2, parag. 1, line 6-11; and page 1145, col. 2, parag. 1, line 22 to col. 3, line 5).

Wobus teaches that the nerve growth factor cause the differentiation of ES cells in vitro to in to neuron-like cells, and enhanced nerve cell differentiation capacity (lines 12-17).

Thomson offers motivation in stating that human ES cells will provide for human transplantation therapies, and that while substantial advances need to be made in the directed differentiation of human ES cells, progress in the directed differentiation of mouse ES cells to neurons, hematopoietic cells and cardiomyocytes has been made (page 1146-1147, bridg. parag.). Motivation comes from Keller teaching that embryoid bodies provide an approach for defining the earliest steps of commitment from respective precursor population (pages 866-867, bridg. sentence).

Claims 8 and 12 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Keller (1995) Current Opinion in Cell Biology 7, 862-869 in view of Thomson et al (1998) Science 282, pp. 1145-1147 and Vittet et al. (1996) Blood 88, 3424-3431 for reasons set forth in the previous office action mailed January 29, 2003.

Keller teaches the production of embryoid bodies by culturing ES cells in the absence of feeder cells or LIF, and to culture them in liquid media or methyl cellulose containing media on bacterial Petri dishes (page 862, col. 2, lines 5-10). The ES cells grown in these conditions will not adhere to the surface of the culture dish, that the ES cells are grown in suspension, and subsequently form EB's (page 862, col. 2, lines 10-13). In some protocols the EB's are dissociated to form a monolayer and grown on stromal cells to develop into hematopoietic lineage cells (page 863, figure 1(b)). This co-culture provides at least one

exogenous factor. Keller teaches that embryoid bodies, when cultured for extended periods of time can generate cells of the hematopoietic, endothelial, muscle and neuronal lineages (page 863, col. 1, lines 5-9). The formation of specific lineages is the formation of specific cell types.

Thomson teaches the production of human embryonic stem cells line, H9 (page 1145, col. 2, parag. 1, line 6-11; and page 1145, col. 2, parag. 1, line 22 to col. 3, line 5).

Thomson offers motivation in stating that human ES cells will provide for human transplantation therapies, and that while substantial advances need to be made in the directed differentiation of human ES cells, progress in the directed differentiation of mouse ES cells to neurons, hematopoietic cells and cardiomyocytes has been made (page 1146-1147, bridg. parag.). Motivation comes from Keller teaching that embryoid bodies provide an approach for defining the earliest steps of commitment from respective precursor population (pages 866-867, bridg. sentence).

Vittet teaches the differentiation in vitro of ES cells into endothelial cells by incubation in the presence of IL-6 and other growth factors (page 3427, col. 1, parag.1, lines 2-6 and 3428, col. 1, parag. 1, lines 1-4).

Claims 8 and 14 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Keller (1995) Current Opinion in Cell Biology 7, 862-869 in view of Thomson et al (1998) Science 282, pp. 1145-1147 and Drab (1997) FASEB Journal 11, 905-915 for reasons set forth in the previous office action mailed January 29, 2003.

Keller teaches the production of embryoid bodies by culturing ES cells in the absence of feeder cells or LIF, and to culture them in liquid media or methyl cellulose containing media on bacterial Petri dishes (page 862, col. 2, lines 5-10). The ES cells grown in these conditions will not adhere to the surface of the culture dish, that the ES cells are grown in suspension, and subsequently form EB's (page 862, col. 2, lines 10-13). In some protocols

the EB's are dissociated to form a monolayer and grown on stromal cells to develop into hematopoietic lineage cells (page 863, figure 1(b)). This co-culture provides at least one exogenous factor. Keller teaches that embryoid bodies, when cultured for extended periods of time can generate cells of the hematopoietic, endothelial, muscle and neuronal lineages (page 863, col. 1, lines 5-9). The formation of specific lineages is the formation of specific cell types.

Drab teaches the differentiation of ES cells into vascular smooth muscle cells by incubation in the presence of retenoic acid and dibutyryl-cAMP (page 913, col. 1, parag. 1, lines 1-3)

Thomson teaches the production of human embryonic stem cells line, H9 (page 1145, col. 2, parag. 1, line 6-11; and page 1145, col. 2, parag. 1, line 22 to col. 3, line 5).

Thomson offers motivation in stating that human ES cells will provide for human transplantation therapies, and that while substantial advances need to be made in the directed differentiation of human ES cells, progress in the directed differentiation of mouse ES cells to neurons, hematopoietic cells and cardiomyocytes has been made (page 1146-1147, bridg. parag.). Motivation comes from Keller teaching that embryoid bodies provide an approach for defining the earliest steps of commitment from respective precursor population (pages 866-867, bridg. sentence).

Applicant argues that references Keller, Wobus, Vittet and Drab are all directed to aspects of in vitro differentiation of murine ES cells, and that none of the references is directed to directed differentiation of human ES cells, the subject matter of claims 8-17. Applicant argues that no reasonable expectation of success exists to apply the techniques of Keller, Wobus, Vittet and Drab to human ES cells because of the differences between mouse and human ES cells. Applicant argues that mouse ES cells have different cell surface markers than those present on human ES cells. Applicant argues that the difference in cell

surface markers renders the differentiation cues different between mouse and human ES cells. Applicant argues that because mouse embryogenesis is much faster than human, the growth factors that influence early embryonic development in mouse cannot be expected to influence human development in the same manner. These arguments are not persuasive.

Applicant has not provided any evidence that the difference between mouse and human ES cells would affect the induction of differentiation in human ES cells by using the protocol of mouse ES cell differentiation. Further, cell surface markers have not been linked as those proteins required for or involved with differentiation. Further, human and mouse ES cells have at least one marker in common, alkaline phosphatase (See Thomson and Marshall, submitted with the response filed June 2, 2003, page 146, Table II.) Further, Thomson (1998), page 1146, col. 1, states that human ES cells form teratomas when injected into SCID-mice, and that the teratomas formed endoderm, ectoderm and mesoderm. Keller teaches that mouse cells from EB's form cells of the endoderm, ectoderm and mesoderm. Thus, if the mouse embryoid bodies, composed of ES cells, of Keller form cells of the same type as the human ES cells of Thompson, there would be every expectation that human EB's would also form the same germ layers.

Applicant argues that in supplied reference, Elsea, that mice produced by gene knockout technology in ESC's to mimic human disease exhibit phenotypes and symptoms not associated with the target disease. Applicant argues that for example, mice designed to be models for Lesch-Nyhan disease did not mimic the disease. Applicant argues that such results emphasize the genetic difference between mice and humans. these arguments are not persuasive.

The results pointed to in Elsea do indicate genetic, physiological and/or metabolic differences between human ES cells. However, at no point does Elsea state that mouse and human ES cells response differently to differentiation signals. With regard to KO technology,

Elsea states that "... many metabolic diseases are relatively easy to recreate in mice through gene knockout technology ..." Elsea goes on to indicate that Lesch-Nyhan disease is not one that is easily produced (abstract). Thus, Elsea indicates that KO technology in mouse ES cells is only sometimes a problem.

Applicant argues that Thomson teaches the production of human ES cells, but does not teach the steps found in claims 8-16 to direct differentiation of human ES cells. Applicant argues that Thomson states that human ES cells are particularly valuable for the study of the development and function of tissues that differ between mouse and human. These arguments are not persuasive.

While Thomson is not a 102 reference, the combination of Keller, Thomson, Wobus, Drab and Vittet provides sufficient teachings and motivation to reach the claimed invention. Thomson was never cited as a stand alone references. Applicant's reference to Thomson (1998) at page 1147, col.1 cannot be found. However, in reference to directing human ES cell differentiation, Thomson states that "progress has been made in the in vitro differentiation of mouse ES cells" clearly implying that mouse knowledge will enhance the development of human ES cell differentiation strategies. There are no teachings in Thomson (1998) that the differentiation protocols for mouse and human ES cells will be different.

Applicant argues that there is no motivation to combine the teachings of Keller, Thomson, Wobus, Drab and Vittet because there is no implicit suggestion of motivation to combine. Applicant argues that the cited motivation is not found when the comments are read context, there is no motivation to use methods for mouse ES cells to direct human ES cell differentiation. Applicant argues that the motivation attributed to Keller does not provide any suggestion or motivation that techniques used in forming embryoid bodies from mouse ES cells are applicable to forming embryoid bodies from human ES cells. These arguments are not persuasive.

With regard to motivation to combine, the court has stated: "reason, suggestion, or motivation to combine two or more prior art references in single invention may come from references themselves, from knowledge of those skilled in art that certain references or disclosures in references are known to be of interest in particular field, or from nature of problem to be solved," ((*Pro-Mold Tool Co. v. Great Lakes Plastics Inc.* 75 F.3d 1568, 1573, 37 USPQ2d 1626,1629 (Fed. Cir. 1996)). There is no doubt that Thomson set forth in the article (1998) that human ES cells will provide therapies for human disease. However, the claims are to very general methods of directing differentiation of human ES cells. For this scope, the comments from Thomson that significant process has been made in mouse ES cells are sufficient motivation to combine. Thomson sates that substantial advances in basic developmental biology are required to direct ES cell efficiently to lineages of clinical importance, and not that such advances need to be made to produce differentiated cells per se. Applicant's claims do not require that the human ES cells be differentiated to any particular degree or extent, just to a specific cell type. Any none ES cell type would be a specific cell type given the lack of a definition of the term. A cell of the mesoderm, endoderm or ectoderm meets "a specific cell type." Further, Keller's statements provide the motivation of using EB as the source of ES cell for differentiation. Thus, Keller provides the motivation to produce EB's from Thomson's human ES cells and differentiate cells from the EB's. The breadth of the present claims permits the application of the art of record.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until

after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 703-308-1126. The examiner can normally be reached on M-Th, 8:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Deborah Crouch, Ph.D.
Primary Examiner
Art Unit 1632

dc
July 31, 2003